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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,696	10/31/2001	Donald Davies	2190/49927	8654

23911 7590 02/24/2005

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EXAMINER	
MARVICH, MARIA	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,696	DAVIES, DONALD	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-54,56,57,59-63,65-76,78,79,81 and 84-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-54,56,57,59-63,65-76,78,79,81 and 84-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment, Declaration and Request for Continued Examination filed 1/24/05. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/24/05 has been entered. The Declaration is discussed further below.

Claims 1-40, 55, 58, 64, 77, 80, 82 and 83 have been canceled. Claims 86 and 87 have been added. Claims 41, 45, 46, 53, 54, 56, 57, 61, 63, 68, 78, 84 and 85 have been amended. Claims 41-54, 56, 57, 59-63, 65-76, 78, 79, 81 and 84-87 are pending.

Claim Objections

Claims 46, 47, 50, 52, 59, 68, 69, 72 and 74 are objected to because of the following informalities: the claims include lists, which are separated by semi-colons. It would be appropriate to separate the items by a comma. **This is a new objection.**

In claim 47, TRP-1, HER2, HER3, ERBB, CEA and MUC1 are abbreviated and should be spelled out the first time these abbreviations occur in the claims. **This is a new objection.** Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 7-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-14, 19-21 and 23-24 of copending Application No. 10/258,760. **This is a new rejection.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 1-14, 19-21 and 23-24 of copending Application No. 10/258,760 because both sets of claims recite methods of administration to a mammal of a polypeptide with p450 activity such as CYP1A2, CYP2E1 and CYP3A4. That is, the cited claims of 10/258,760 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, the instant claims recite that the target is cell killing of cancer cells, while application 10/258,760

recites that the target is a non-cancer cell. Absent evidence to the contrary administration of a vector encoding a p450 enzyme accompanied by acetaminophen leads to non-discriminatory killing and therefore, non-cancer and cancer cells would be expected to be subject to cell killing.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding a patent from 10/258,760, then two different assignees would hold a patent to the claimed invention of 10/258,760, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 recites the limitation "composition" in claim 64. There is insufficient antecedent basis for this limitation in the claim. Claim 64 has been cancelled. **This is a new rejection necessitated by applicants' amendment.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-54, 56, 57, 59-63, 65-76, 78, 79, 81 and 84-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer in a non-human comprising administration to a mammal of acetaminophen and a vector comprising a polynucleotide encoding CYP1A2, CYP2E1 or Cyp3A4, does not reasonably provide enablement for treating cancer in a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a composition comprised of acetaminophen and a vector encoding CYP1A2, CYP2E1 or Cyp3A4 and methods of using these compositions to treat cancer. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention**. The vector comprises polynucleotide sequences encoding a polypeptide selected from the group consisting of CYP1A2, CYP2E1 and CYP3A4, which

converts acetaminophen into a metabolite called N-acetylbenzoquinoneimine (NABQI). Exposure of cancer cells to this enzyme in the presence of acetaminophen leads to an increase in NABQI leading to cytotoxicity. Normal liver cells have higher levels of glutathionine, which reacts with NABQI to convert it to a non-toxic substance. The invention further recites methods of decreasing glutathionine in the cancer cells, directing the vectors encoding the enzymes specifically to cancer cells and by addition of furaphylline to inhibit human CYP1A2 while administering rodent or another non-human forms of CYP1A2.

The method is directed toward gene therapy in mammals and humans using gene delivery protocols such as viral vector delivery. The only disclosed utility for practicing the claimed methods is for gene therapy. These steps of gene therapy using a viral vector in humans exacerbate an already complex method.

3) **Number of working examples and guidance**. The disclosure teaches the administration of CYP1A2 in the presence of acetaminophen in *in vitro* cell systems. The instant examples are directed to methods of establishing stable and transient cell lines expressing p450. Experiments with transfected COS and H1A2 MZ cell lines demonstrate that *in vitro* acetaminophen in the presence of CYP1A2, leads to cell death. Variable bystander effects were identified in several cell lines incubated with stably expressing H1A2 MZ cells.

The instant specification fails to demonstrate any examples or specific guidance for introduction of the composition comprising a vector encoding a polypeptide having p450 activity and acetaminophen into a mammalian subject. While guidance for administration of polynucleotides to a subject are provided, the guidance is broad and general i.e. administration includes but is not limited to intravenous, intramuscular, intraperitoneal injection or direct

injection into the tumour tissue (page 10, line 21-24). There are no disclosures for *in vivo* concentration of vector or acetaminophen, no dose schedules and no determination of subjects for which the method would be directed.

Applicants provide in a Declaration evidence that using the methods of the instant invention in a variety of *in vitro* tumor cell lines, the cells are sensitized to cell killing following administration of Ad vectors expressing human or mouse CYP1A2 and acetaminophen. Also applicants demonstrate experimentally that the levels of glutathionine can be modulated using buthionine sulphoximine leading to improved cell killing. As well, furafylline selective inhibition of hCYP1A2 over mCYP1A2 is demonstrated. Applicants also provide an *in vivo* model system to demonstrate that the methods of the instant invention reduce tumor size. Adenoviral vector expressing mouse of human CYP1A2 as administered to HepG2 xenograft Balb/C mice in the presence of acetaminophen or paracetamol.

4) **State of Art**. The art of gene therapy for the treatment of cancer is a high art. Enormous efforts have been directed toward the development of gene therapy vectors and for cancer treatments. Each goal alone is complex and requires great skill in the art.

5) **Unpredictability of the art**. The art of the instant invention is unpredictable for treatment of cancer in humans. First, is the method of delivery of the polynucleotides. This has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al (Verma et al. Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression".

To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols.

The invention specifically recites use of viral vectors for delivery, which in itself is highly unpredictable in the art. Tropism of the viral vectors does not result in targeted administration of the composition. Meng and Deiry (Gene Therapy of Cancer, 1999, page 6, column 1) teach that means of delivery other than intratumoral injection compound the obstacles associated with adenoviral use. "Tropism for organs such as liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous of the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass". "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, p 1165, column 2). Therefore, it is unpredictable that administration of the composition will lead to targeted delivery to the appropriate sites.

Secondly, the level of infection necessary to achieve therapeutic affects of the heterologous gene without toxicity to normal cells that results from leaky expression of the viral genes required for replication is unknown. Given the unpredictability of directed delivery, bystander killing would result in surrounding cellular death. Finally, as noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other

cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments. No viral vector has proven adequate sources of gene delivery vehicles to date.

Finally, applicants have provided evidence *in vitro* and *in vivo* in a Declaration by Donald Davies filed 1/24/05 that the methods of the instant invention lead to enhanced cell killing. However, the ability to predict the potential for success in humans based upon these results is highly unpredictable. While *in vitro* cell culture and *in vivo* animal models have been provided as evidence of success of treatment, these results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the *in vitro* transfection systems and the human disease state. A study by National Cancer Institute demonstrated that using xenograft models do not handle drugs in the same way that the human body does and cell culture provides no information about whether a drug will make it to target sites or not (see e.g. Gura, Science, page 1041, col 1). Ultimately the xenograft model system identifies agents that are effective in treating mice but not humans (see e.g. page 1041, col 2, last paragraph).

6) **Summary**. The invention recites a complex series of methods for the treatment of cancer using a vector CYP1A2, CYP2E1 and CYP3A4 and acetaminophen. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict successful administration of the compositions: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Amendment-35 USC 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on pages 14-17 of the amendment filed 1/24/05. Applicants' arguments are based primarily upon the Declaration by Donald Davies filed 1/24/05 which is said to demonstrate with its positive in vivo data that the theoretical difficulties in gene delivery are not applicable to the method of the instantly claimed invention and therefore no undue experimentation is required to determine effective doses and delivery routes. The *in vivo* and *in vitro* date has been summarized above.

Applicants' arguments filed 1/24/04 have been fully considered but they are not persuasive. Applicants have demonstrated that using an *in vivo* Applicants' recite that viral vectors can be used to deliver the nucleic acids into the cells. As stated above, no viral vector has proven adequate sources of gene delivery vehicles to date. And use of viral vectors is "not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled

artisan can make and **use** the claimed invention for the recited treatments". Applicants claim a method of treating all cancers in humans. The necessary information to identify the appropriate means of delivery of the polynucleotides and means of delivery to the tumors as well as proper schedules of infection and dosages are unknown. Given the lack of guidance in the specification and the prior art , it is concluded that a person of skill in the art would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER

February 16, 2005